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Thesis

THE STRUCTURE, FUNCTION, AND PATHOLOGY OF THE THYROID GLAND

Submitted by

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THE STRUCTURE, FUNCTION, AND PATHOLOGY OF THE THYROID GLAND

The Structure, Function, and Pathology

of the Thyroid Gland

Dissection of the Thyroid Body and of

The Parts in Immediate Relation to it.

"Textbook of Anatomy", edited by Cunningham, 2nd and revised ed., p. 1216.

THE STRUCTURE, FUNCTION, AND PATHOLOGY OF THE THYROID GLAND

I. STRUCTURE AND DEVELOPMENT

A. ANATOMY

1. Gross morphology and its relationship

The thyroid gland is a reddish yellow, lobulated, U-shaped structure, which is divided into right and left lobes. The lobes are joined together in the median line by an isthmus. The thyroid gland is named after the thyroid cartilage on account of its shield-like shape.

The gland is situated in the middle third of the neck and partially encloses the trachea laterally close to the thyroid cartilage. The ventral surface is covered by the infrahyoid muscles, the cervical fascia, and the skin. The dorsal surface is related with the first two to four rings of the trachea, cricoid cartilage, esophagus and pharynx, common carotid arteries, vagus nerves, and other structures. It is held in place by a fairly strong capsule connected with the cervical fascia. The capsule contains two layers, an outer, which can be easily removed, and an inner layer, which adheres tightly to the gland.

The isthmus of the thyroid gland is frequently absent, and, even, when present, it is difficult to palpate, owing to fobrosis. Usually, under normal conditions, the gland itself cannot be felt at all. The right lobe is often larger than the left and in man, the lobes are about six centimeters long. A pyramidal process often extends cephalad from the isthmus, on the left side usually, and it may even reach as far as the foramen cecum, at the base of the tongue. In very rare cases, the process may be double, and extend on either side of the middle line, Accessory thyroids

sometimes occur near the hyoid bone.

The weight of the thyroid gland is very variable, a good average being about 35 grams. It is sometimes larger in some localities, due to altitude, climate, and other factors. Normally, the gland is one-fourth larger in women than in men. The increase in weight may be due to pregnancy, hyperemia, or increase colloid formation.

The variability of the thyroid gland is probably due to several factors. There are three potential variables from the standpoint of origin, the median and the two ancestral lateral anlagen. The great changes in position, when the organs of the neck and of the thorax are developong, offer an opportunity for variation. Another favorable factor for variation may be due to an absence of a duct which should anchor the gland to the alimentary canal, combined with the fact that the tissue can function equally well in almost any part of the neck region.

The microscopical appearance of the thyroid unit, the alveolus, is similar in all animals, from fish to man. The alveoli in general, are either round or oval, consisting of closed spaces lined with a single layer of low cuboidal epithelium. The high cuboidal or columnar cells are said to always indicate hypertrophy(Marine, 1922). The cells are quite regular in size, although one can often distinguish the so-called chief cells from the colloid cells. These cells probably represent the different stages of secretory activity.

All the alveoli are filled with a glairy, amber-colored viscid globulin, a colloid, which gives to the thyroid its specific chemical and physical characteristic. This colloid contains the active substance of the gland, an iodin compound which Kendall (1915) isolated in the pure form and named it thyroxin. It is believed to be the only medium for storing this very active substance in an inert manner. It is not until after birth,

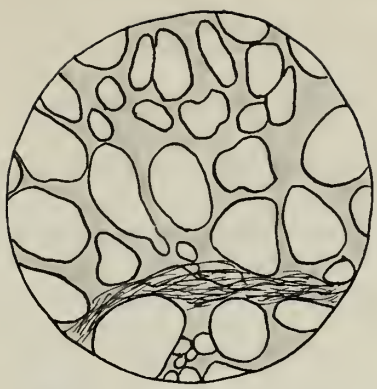
however, that a considerable amount of colloid material is formed within the follicles, and iodin may be detected chemically in the gland.

The colloid secretion lies in contact with the free border of the epithelial cells and completely fills the alveolus, save for occasional vacuole-like areas. It is homogeneous and stains readily with acid dyes. The colloid of the adjacent alveoli varies in consistency and staining intensity. Capillaries rich in lymph and blood supplies form the network which anastomoses about each alveolus and come into very close relation with the epithelial lining. In the normal human thyroid, especially in early fetal life, there are groups of undeveloped thyroid cells, called "thyroid rests", which lie in the stroma between the developed alveoli. In the stroma are normal lymphoid cells whose foci may undergo marked changes under conditions of generalized lymphoid hyperplasia as in myxedema, Addison's disease, exophthalmic goiter, and status lympaticus. (R.R. Bensley, Cowdry, Major, Marine, and Simpson).

2. Blood supply

The surface of the thyroid is penetrated by arteries and veins and the gland is therefore, very rich in blood supply. The superior thyroid arteries coming from the external carotids run to the apex of each lobe and give off numerous branches, which ramify over the ventral and medial surfaces and penetrate into the glandular material. These arteries sometime unite at the isthmus. The inferior thryoid arteries, may be as large ar larger than the superior thyroids, spring from the subclavians and run on the lateral surfaces of the gland. They are intimately related to the superior and inferior parathyroid glands. Frequently, a thyroidea ima artery arises from the arch of the aorta and runs to the isthmus.

The blood leaves the thyroid through numerous veins which form



Normal human thyroid showing trabecula and its relation to stroma.

"Endocrinology & Metabolism", 1922, Vol.I, page 273.

Colloid goiter in man (from case of clinical exophthalmic goiter), illustrating the lymphoid hyperplasia, the irregular size of the alveoli, uniform colloid and low cuboidal epithelium. (After Marine and Lenhart, Arch. Int. Med., 1911:7).

a dense plexus beneath the capsule. The superior thyroid veins leave the ventromesial surfaces of the lobes and open into the internal jugular veins. The middle thyroid veins run laterally to enter the jugulars. After forming a plexus on the ventral surfaces of the trachea, the inferior thyroid veins, leave caudally and pour the blood into the left innominate vein. Occasionally, a thyroidea ima vein may occur, corresponding to the artery of the same name, and discharges its contents into the left innominate. All the veins are said to be without valves.

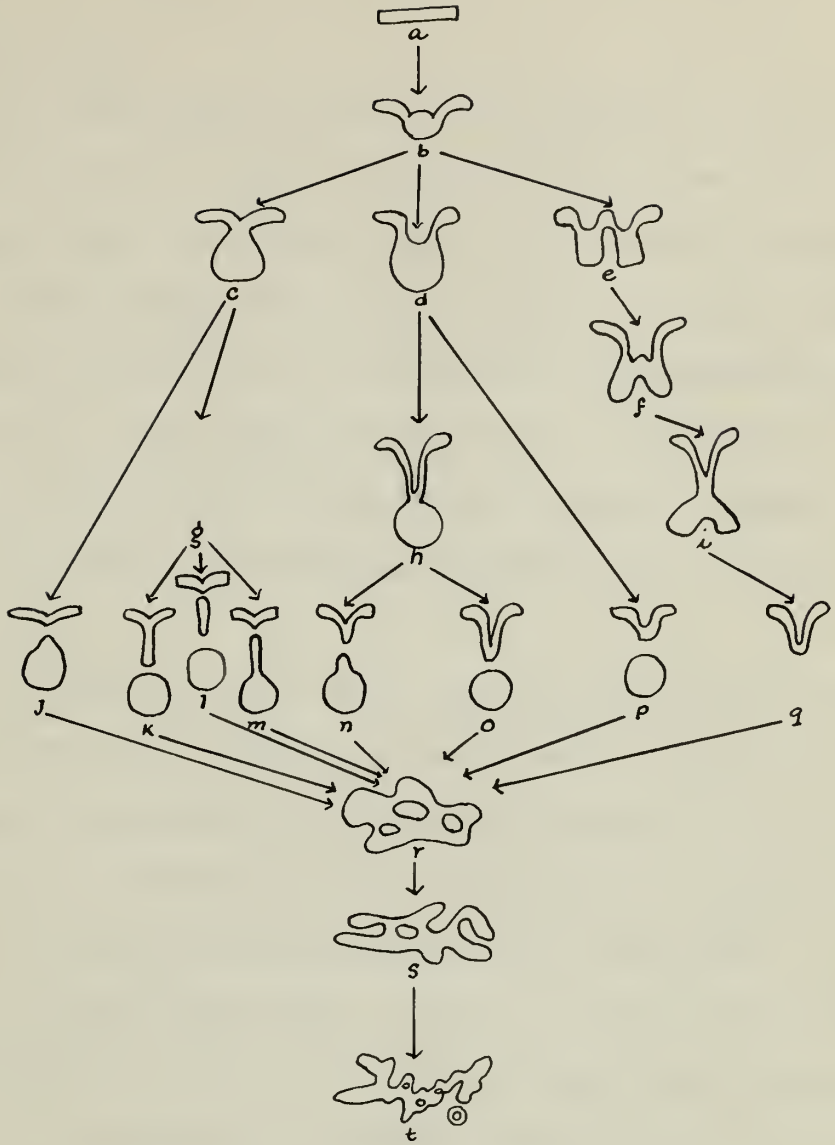
B. EMBRYOLOGY

1.Early development

The thyroid gland begins to develop very early as a median evagination of the endoderm of the floor of the pharynx between the first and second pair of pharyngeal pouches. The following passages are quoted from Cowdry (1922) who explains the diagram published by Norris in 1918, to demonstrate the stages of development and the variations that are likely to occur. "The development may take place in three directions: the downgrowth may be solid (c), or possess a hollow stalk (d), or be double (e)". The last condition is rare in the higher forms of animals.

"The stalk connecting the glands with the pharynx now elongate, so that the conditions represented in (g), (h) and (i) are brought about.

"With complete separation from the pharynx, in embryos of from about four to seven millimeters, a number of variations arise, as is illustrated in diagrams (j) to (q). Division may occur near the stalk in association with the thyroid body, thus favoring the formation of a pyramidal lobe or thyroglossal duct; and, conversely, the development of "lingual rests" and "suprahyoid bodies" result when separation takes place near the



Scheme of the development of the human thyroid gland,
after Norris. "Endocrinology and Metabolism",
Vol.I, 1922, p.211.

body of the thyroid, leaving a larger amount of tissue in association with the pharynx.

2. Cavitation

"The next change consists in the formation of closed cavities within the gland mass (r), which, according to Norris, are quite independent of the original lumen of the thyroid pouch. He attributes considerable importance to these intraglandular spaces, because he has also found them in approximately the same stage of development in representatives of several classes of animals. These sapces finally open to the periphery of the gland anlage (s), and the definite follicular cavities begin to appear in their walls (t)". (E.V.Cowdry, "Endocrinology & Metabolism", I, p. 210).

3. Growth

According to Jackson (1909) "the thyroid increases slowly but steadily in relative size during the prenatal period". After birth the gland decreases in relative size progressively, though its absolute weight increases. Numerous observations have been made on the subsequent growth of the thyroid in man, but they are scattered and uncorrelated. (Cowdry,1922) The only animal whose thyroid growth phenomena are being standardized is the white rat, and this was made possible chiefly through the researches of Donaldson and his associated at the Wistar Institute (1906). Hatai (1913) and Jackson (1916) bothe agree that there is no difference in weight of the thyroid gland of the male and female rats. This is an interesting result, because in man, the male thyroid is generally believed to be relatively lighter in weight than the female organ.

Donaldson has made some comparative studies on the laws of growth in the rat and man. There seem to be many points of similarity, but since the weight of the gland is so dependent upon the amount of stored colloid, there is always this element of error to be considered in the comparisons, either

by weight or by volume, with other ductless glands. Bensley (1916) has proposed a laborious but a valuable method to estimate the relative amounts of parenchyma and colloid; sections are photographed, after which tracings are made on cardboard of the contained parenchyma and colloid, and then these are cut and weighed. By this method he is able to obtain a ratio.

Feeding experiments have been performed by Jackson (1916) upon white rats to get some idea of the growth energy of the thyroid gland. He fed them just enough to keep the body at a constant weight. This treatment produced a well defined loss in the weight of the thyroids as compared with that of the hypophysis and suprarenals, which showed a considerable increase. Castration, likewise, brings about a similar reduction in the rate of growth of the thyroid and increase in the suprarenals and hypophysis (Schäfer, 1912). Retrogressive changes which normally occur in the gland as the age of the individual advances, are characterized by a relative increase in the connective tissue at the expense of the secretory epithelium.

II. VIEWS CONCERNING THE FUNCTION OF THE THYROID

A. EARLIER VIEWS

In Todd's "Cyclopedia of Anatomy and Physiology", published 1849 to 1852, is found an interesting article written Handfield-Jones. It deals with the history and development of knowledge of the thyroid at the time at which the article was written.

1. Galen

It is likely that Galen was referring to the thyroid when he thus described the glands in the region of the larynx : "These are

always found more loose and spongy than others, and ----- have been created for the purpose of moistening and bathing all the parts of the larynx and the passage of the throat".

These statements showing Galen's knowledge of the lack of ducts in the thyroid gland are quoted by Morgagni: "Now the neck has two glands in which moisture is generated. But from the two glands which are in the neck there come forth no vessels by which the moisture may flow out, as those do from the glands of the tongue".

2. Wharton

A Yorkshireman, Thomas Wharton, in 1656, marked an epoch in the history of anatomy by publishing his own discovery of the duct of the submaxillary gland. Besides this, he gave careful descriptions of the salivary and thymus glands. The results of his discovery were first put forth in his lectures at the College of Physicians in 1652.

He described fully the anatomy of the thyroid gland and observed that it had more blood supply than any other gland. Wharton gave the organ its name from the Greek word meaning a shield, by which it has been known since. The functions suggested by Wharton are: (1) to take up the superfluous moisture from the recurrent nerve; (2) to "cherish" the cartilages; (3) to lubricate the larynx and render the voice more sweet; and (4) to contribute to the contour and beauty of the neck. Galen favors the third function ascribed by Wharton, and it was a popular idea for a long time.

3. Verheyen and Santorini

Verheyen and Santorini doubted the presence of a duct leading into the pharynx and trachea.

4. Haller

In 1776, Haller dismissed the question of a duct in the thyroid, and classified the thyroid with the thymus and spleen as glands without ducts which pour a special fluid through the veins into the general circulatory system. This idea is similar to the modern conception of the thyroid gland.

5. Simon

Papers as late as 1834 showed that the economy of the thyroid was scarcely known or even suspected. About ten years later, in 1844, Simon presented an interesting theory which has been recently revived by V. Cyon. Simon attributed to the thyroid a regulatory function on the blood supply to the brain and that it exerted its secretory function in an alternating manner with the substance of the brain.

B. LATER VIEWS

1. Philipeaux, Drobnick, and Munk

Philipeaux (1884), and Drobnick (1888), and Munk (1897), and some other investigators are inclined to deny the supreme importance of the thyroid in the animal economy. They attributed the untoward symptoms recorded by the other workers to nerve injury --- a disturbance of nutrition in animals without thyroid may often be observed in those which have not been operated upon. Out of four monkies operated on in England, only one was sent to him as "myxedematous". The animal had nothing more than a facial swelling and, according to Munk, was otherwise in good health and lived ten months after the operation; he, therefore, insists that the thyroid is not absolutely essential to life, though its removal is a dangerous operation.

2. Murray

Murray (1900) concluded from his various experiments that the function of the thyroid is to supply an internal secretion which is essential to maintain the normal metabolism of the body. The parts especially concerned are that of the central nervous and cutaneous systems in the adult, and of the growing bones of the young. This internal secretion is passed by the veins or lymphatics into the general circulation.

3. Vincent and Jolly

The general conclusion reached by Vincent and Jolly (1904 & 1906) are that neither the thyroid nor the parathyroids can be considered as absolutely essential to life, for some animals do not show any suffering at all after an extirpation.

III. EXTIRPATION EXPERIMENTS

A. UPON ANIMALS

The earliest extirpation experiments seem to have been performed by Raynard, in 1834. He stated that the treatment for goiter in dogs can be carried out just as in man. The complete removal of the thyroid resulted in the death of the young animals within a few days, while in the middle-aged and old dogs, the experiment was successfully carried out. The post-mortem examinations of the young dogs did not reveal the cause of death.

The thyroid was removed from a dog and a goat without producing any ill effects by V. Rapp (quoted by Bopp, 1840), but the removal of a goiter from dogs proved rapidly fatal. During the years 1856, 1857, and 1858, Moritz Schiff performed a series experiments upon dogs, cats, and rats;

but a few days after the operation, the animals died.

Cretinism has long been recognized and in 1874, Gull, described the condition which Ord, in 1878, called "myxedema". The symptoms of "cachexia strumipriva", or "operative myxedema", were noted by Swiss surgeons in 1882 after they had operated upon human subjects for goiter. Schiff's earlier works were overlooked for many years, for after he had read the results of his experiments before the Royal Academy of Science in Copenhagen, he buried himself in a work on the formation of sugar in the liver. It was not until 25 years later, that Schiff, spurred on by the observations of Kocher and Reverdin in Switzerland, took up the problem again.

In 1884, he recalled his earlier experiments of 1856-1858, and published the results with his new series of investigations. Thyroidectomy in the rat and the rabbit was not followed by any serious results, but complete removal, in the cat and the dog, however, proved fatal. He gave a very good account of the symptoms of the nervous condition of the dog after the thyroid was removed, and stated that these symptoms may be avoided by a previous graft of the thyroid of one dog into the abdominal cavity of another. Schiff also observed such symptoms as general malaise, arrest of growth in a young cat, and in two cases of edema. Some of the symptoms observed, particularly those of a nervous nature, are at present attributed to the loss of parathyroid tissue at the time of the operation.

Wagner, in 1894, found an increase response in the nerves to galvanic currents when the thyroid and parathyroids were removed in cats.

Thyroidectomy was also performed on monkeys. Horsley (1896) noted fibrillary twitchings of the muscles a week after the operation and that on voluntary movement of the muscles, the twitchings ceased. The animal then became a "cretinoid" and there was a "myxedematous" condition of the subcutaneous tissues. By keeping the animal warm the tremors were

relieved. According to Horsley, the swellings seen on the skin of the face and the abdomen, are due to the infiltration of mucin into the tissues. The parotid gland produced large quantities of mucin and the salivary glands became enormously hypertrophied.

During the succeeding years a number of experiments were carried. The majority of these confirmed the general views of Schiff(1884) on the effects caused by the extirpation of the thyroid. It is possible that the separate functional importance of the parathyroids was not known at this time. The thyroids and parathyroids were always removed together in cats, dogs, and monkeys, while in the herbivora the two external parathyroids were left behind in what was called "total thyroidectomy". Although the external parathyroids were discovered by Sandström in 1880, and by Baber in 1882, it was not until 1891, that Gley rediscovered them and demonstrated their functional importance in his experiments with rabbits. (Vincent, 1922).

Many investigators disagree on the importance of the presence of the thyroid gland to the life of an animal. (Philipeaux, Munk, Drobnick, and others). Munk (1897) insists that the gland is not essential to life, though the removal of it involves a dangerous operation.

Vincent and Jolly (1904 & 1906) also concluded that "neither the thryoid nor parathyroids can be considered as organs absolutely essential for life. Rats and guinea-pigs do not seem to suffer at all as the result of extirpation. Monkeys show only transient nervous symptoms. Dogs, cats, foxes and prairie wolves frequently suffer severely and die. On the other hand, badgers do not appear to be affected by the operation.

"In no animals, not even in monkeys, have we been able to induce any swellings of the subcutaneous tissues, which is the most striking feature of myxedema in the human subject. We think, therefore, that the pathology

of myxedema in the human subject must be more complex than simple thyroid insufficiency". (Vincent and Jolly, Some observations upon the functions of the thyroid and parathyroid glands; Journal Physiol., 1904, XXXII, 1906, XXXIV; Lond.)

Experiments have been carried out with animals of varying age, and it was proved by Sutherland Simpson, in 1913, to be an important factor in the extirpation experiments. He found no apparent ill effects in the removal of the thyroid with the contained internal parathyroids in 13 adult sheep and 16 lambs, seven to eight months old; but, in a similar operation of three lambs about two months old, "typical cretins" were produced.

In 1916, Basinger carried out an intensive research in thyroidectomy in rabbits. Out of 140 animals operated upon, 86 were found to be "typical cretins". The experiments were carefully controlled as to feeding and selection of subjects and normals from the same litters. The body weight was about 175 grams when the thyroidectomy was performed, the animals being two to three weeks old at that time.

After two weeks the appearance of cretinism was detected. The bones were short and the muscles of the limbs were too weak to support the weight of the body. A pseudo-rickety condition was shown in the development of the bones. The posture was typical of cretins; the skin was dry and scaly, and finally became eczematous. These animals also developed the typical "pot belly" condition of human cretins, but there was no evidence of the typical human myxedema in them. The chronic progressive cachexia described by Hofmeister (1894) did not appear in any of these specimens after they had been kept alive for a year.

The condition did not show any apparent effect even after a transfusion of normal blood serum into the cretins. A transfusion from thyroid-fed rabbits, however, brought about some improvements. Feeding the

aniamls with desiccated thyroid substance markedly improved the symptoms, but it failed to bring about an entirely normal development. When the treatment gas discontinued a relapse resulted. The cretins proved to be more susceptible than normal rabbits to the toxic action of thyroid feeding.

From the experiments it can be seen that cretinism resembling that of human beings can be induced in young animals by the complete removal of the thyroid when one or more of the parathyroids are left behind. The symptoms, however, may not be observed in the older animals.

According to the experiments carried out by Edmunds (1916), cataract is frequently produced in dogs as a result of a complete extirpation of the thyroid and parathyroid glands. In some animals one can observe a complete disturbance in growth and development. Thyroidectomy in amphibia will interfere with their normal metamorphosis, the growth and ossification of their bones may be retarded or completely stopped. Hoskin, Terry, and Allen (1916) did not find any hindrance in the development of the gonads.

B. UPON MAN

It is clearly shown by experimental thyroidectomy in animals that the presence of the thyroid is necessary to prevent the more severe manifestations of hypothyroidism. The experiments performed by various investigators have shown that a large variety of animals are now known to develop cretinic characteristics after thyroidectomy. Typical cases of cahexia strumipriva are at present rare in human beings since the retention of a certain amount of thyroid is recognized as being essential for normal thyroid function. Occasionally the remaining portion of the gland atrophies, thus bringing on a complete myxedema. More often, if too much of the gland is removed, a mild hypothyroidism develops. In children, a complete

surgical removal of the gland is followed by cretinism without exception.

The classical case of a child 10 years old, is quoted by most writers. The case is recorded by Bruns. The operation was performed by Sick, 1867, in which the entire goiter was removed from a boy of ten years. When the subject was examined by Bruns eighteen years later, he had developed typical cretinism. The bodily development had been arrested from the time of the operation. The face expression was iodiotic, and there was marked subcutaneous tissue swellings, especially of the eyelids and lips; the skin was dry, and the hair was scanty. The mental capacity of the subject was less than that of a child of ten, his speech was low and he was unable to do any work. Murray (1900) says "that the case was one of advanced secondary cretinism readily explained by the fact that neither before nor after death could any trace of thyroid tissue be found". ("Diseases of the Thyroid Gland", page 21). Kocher (1906) also reports similar disastrous results of complete thyroidectomy in childhood.

IV. TRANSPLANTATION EXPERIMENTS

Innumerable transplantation experiments have been performed with the thyroid, but the literature does not reveal many that are completely successful. The majority have been unsuccessful, due to rapid degeneration and disappearance of the grafted tissue. In some cases when regeneration has taken place, the grafted thyroid tissue has lived and seemed to function for several months.

A. HETEROPLASTIC TRANSPLANTATION

This type of transplantation has always been unsuccessful. The process involves the grafting of the thyroid tissue of one animal into another of a different species.

B. HOMIO TRANSPLANTATION

Homio transplantation is the grafting of tissue from one animal into another of the same species. Vincent (1922) says that this can be successful only in a small number of cases.

C. AUTO-TRANSPLANTATION

In auto-transplantation, the pieces of thyroid tissue of an animal are grafted into different regions of the same animal. This method has proved to be possible by Cristiani (quoted by Vincent, 1922), who, found the grafted tissue active for a long time.

D. SYNGENESIOPLASTIC TRANSPLANTATION

The transplantation of tissue into nearly related individuals of the same species has been given the name "syngenesioplastic" by Loeb (1918). The experiments were performed on guinea pigs, and the results were intermediate between those obtained after homio and auto-transplantation. The tissue remains for a while like the auto-transplanted type but is soon destroyed by lymphocytic infiltration.

Entire glands or lobes of the thyroid have been grafted by the vascular suture method by Carrel and Guthrie (1905 and 1906). The thyroid was removed from its original place and then replaced in the neck. The gland functioned normally after the blood vessels anastomosed and circulation was set up. Other investigators, by using this method, have found success in

some of their experiments. (Thyroid Transplantation by Vincent, Barker's "Endocrinology", I, 1922).

V. RELATIONSHIP WITH OTHER INTERNAL ORGANS

Evidences are more extensively and better established in the relationships between the thyroid gland and other endocrine structures than any of the other organs of internal secretion. (Hoskins, 1922). Numerous experiments have been performed and the summaries of some of the investigators will be given here; however, there is very little concrete knowledge available on which to base definite conclusions.

A. RELATION BETWEEN THYROID AND SUPRARENALS

R. G. Hoskins, in 1910, administered thyroid material to experimental animals, by feeding young guinea pigs 5 to 15 mg. of desiccated thyroid for the first fifteen days of their life. At the end of this period, the animals were killed and their suprarenals were weighed. The animals that were fed with thyroid material averaged 25% heavier than those of the normal controls.

In 1913, Iscovesco, prepared an ether soluble material from the thyroid gland. When he administered this hypodermatically into rabbits, Iscovesco found a considerable degree of hypertrophy of the suprarenals.

A careful study of the effects of thyroid feeding material to albino rats was made by E. R. Hoskins (1916). He observed that the suprarenals were considerably larger in the experimental than the control series. In the younger females the enlargement amounted to 14.5%, and in the older females to 16.1%. The increase in the younger and older males was 36.4% and 38.1%, respectively.

Herring (1917) obtained more marked hypertrophy of the suprarenals than Hoskins by using larger doses of the gland material. He says that "the suprarenal bodies are constantly increased in size by thyroid-feeding both in the male and female rats. The increase is a rapid one------the administration of 0.2 grm. thyroid daily to young male rats has brought about an increase of 73 per cent. in weight per 100 grm. body weight in eight days.

"The general averages show an increase of 56 per cent. per 100 grm. body weight in the males, and an increase of 41 per cent. per 100 grm. body weight in the females as the result of thyroid-feeding. The increase in weight is partly of medulla but chiefly of the cortex". (Quart. Jour. Exp. Physiol., Lond., 1917, XI, p. 232).

In the male rats, Herring observed that thyroid feeding increases the adrenalin content absolutely, but diminishes it relatively to the percentage weight of the suprarenals. The increase of adrenalin in the suprarenals of female rats resulting from thyroid feeding is less constant. In the female rats which thrive well under the influence of thyroid the adrenalin is increased, but in those animals which show checked growth and other toxic symptoms the amount of adrenalin is actually decreased.

The results of the previous investigators were confirmed by Hewitt, in 1920, with additional observations made upon young rats after thyroid feeding was discontinued. There was a tendency for the suprarenals to regain normal weight.

Conflicting results were obtained by Kuriyama (1918). He failed to observe any significant hypertrophy of the suprarenals after thyroid feeding, either with large doses for a short time or small doses over a longer period. He detected no difference in the epinephrin content of the glands. Herring (1920) suggested the various possible errors in Kuriyama's

experimental methods:

1. The desiccated thyroid material used by the investigator was of unknown activity and in doses which would be toxic if fully active,

2. The animals used were markedly different in ages and weights,

3. The females and males instead of being separated were experimented upon together,

4. The dietary factor should be considered. His animals received only dog biscuits and lard paste. They probably suffered from vitamin deficiency, a condition which was proved by McCarrison and others to bring about abnormalities in the adrenals.

A number of investigators also studied the effect of experimental thyroid deficiency. In 1894, Hofmeister performed thyroidectomy upon many young rabbits and studied the results in the various organs. There were no significant differences found between the suprarenals of the experimental and normal animals. Benson (1902) obtained definitely negative results. Most of the investigators who have studied the results of thyroidectomy have devoted very little attention to the suprarenal glands.

In 1913, Tatum removed the thyroid glands from young rabbits two to three weeks old, leaving their inferior parathyroids intact. The operation brought on hyperplasia of the suprarenal medulla and an increase of lipoid material in the cortex.

Carlson stated, in 1914, that "after complete thyroidectomy we invariably get a hypertrophy of the suprarenals to two or three times their normal size". Gley and Quinquaud (1914) in the same year reported a marked increase in the relative weight of the adrenals of rabbits after thyroidectomy. The increase is interpreted as an indication of degeneration rather than of hyperfunction. Herring (1916), however, failed to obtain any significant

effect upon either weight or epinephrin content of the suprarenal glands of five thyroidectomized rabbits.

The experimental results obtained by Stewart and Rogoff (1921) were that the average weight of the adrenals of twenty-five thyroparathyroidectomized rabbits was considerably greater than the normal. The amount of epinephrin was proportionate in both conditions according to per unit weight.

According to R. G. Hoskins (1922), "the study of clinical cases of thyroid disorders has not contributed any significant data on the thyroid-suprarenal relationship". The weight of the evidences, although by no means conclusive, "seems to indicate that the thyroid stimulates the suprarenals."

B. RELATION BETWEEN THYROID AND SEXUAL ORGANS

The reproductive glands produce both internal and external secretions. The external secretion is said to contribute to the reproduction of the species, while the internal secretion is claimed to contribute to the molding of the species. (Harrow, 1922). Though the two secretions cannot be sharply separated, we are here more concerned with the internal secretion which is developed by the "interstitial cells".

Clinicians have long recognized that the thyroid exerts an important influence upon the sex glands. In the cases of Graves' disease, sex functions are often affected. In 1909, Sattler stated the observations of many clinicians of menstrual disturbances occurring during Graves' disease. In Trousseau's experience, all cases showed anomalis. In the 28 cases observed by Griffith, six were amenorrhea cases. West had 38 cases, and most of these showed irregularity. Russell reported 48 cases, menstruation was regular in most instances. In Murray's 170 cases, 45 showed irregularity. By the reports of these investigators, it is evident that there are

many conflicting results; but these indicate that menstrual disturbances are at least not infrequent. The more significant fact is that actual atrophy of the gonads occurs in this disease.

Experimental and clinical hypothyroidism results show a pronounced sex depression. Gandy (1906) illustrated this characteristic very convincingly in his description of his two male clinical cases. Two men, 25 and 33 respectively, after having attained a normal adult sexual condition, developed myxedema, which resulted in a reversion of sex glands to an infantile condition. There are many similar cases on record.

An interesting observation was made by Simonton (1916) in which he reported that about half of the female population, and some of the males of Cumberland Valley, Pennsylvania, suffered goiter. Subnormal genital development was observed in both sexes, and in the women it was followed by menstrual irregularities. The depressed condition was much improved by the administration of thyroid preparations.

The depression of sex functions followed by the degeneration of the gonads after thyroidectomy is so well known that many recent investigators do not consider it worth while to report more specifically in regard to this matter. Whether the thyroid exercises a direct influence upon the reproductive organs or not is not yet definitely known. It is well known that any process that retards the general metabolism is likely to induce sex depression, while any general bodily stimulant will bring on an increased sex activity. H. G. Hoskins (1922) states that it is "quite possible therefore that the sexual manifestations in various thyroid perturbations are merely conditioned by the general metabolic reactions. In any case, however, the end result is the same, whether the effect be mediated directly or indirectly". Castration does not seem to have much effect

upon the thyroid, though it has been stated that a hyperactivity of the latter rarely results in exophthalmic goiter.

C. RELATION BETWEEN THYROID AND THYMUS

The thymus is an organ below the thyroid and behind the upper part of the sternum. It is considered to be of special importance in the early life of an individual, though the general opinion at present is that it functions throughout life. The function of the thymus is a matter of constant debate; some scientists even question that the thymus is an endocrine gland.

Attention has been called to it in connection with various disorders of internal organs. It is well known that in Graves' disease the thymus is much enlarged, a condition which was apparently first noticed by Cooper in 1872. An attempt was made by Capelle (1908) to analyze the literature to determine how frequently thymus hypertrophy occurs in thyroid disorders. He was able to collect 60 cases of Graves' disease with their autopsy records; thymus hypertrophy was noted in 44% of the patients who died of an intercurrent affection; 82% in those who died directly of the disease; and 95% of those succumbing to the operation.

Histological studies were also made upon the thymus glands of three persons who suffered from Graves' disease and general status lymphaticus. Pappenheimer (1910) concluded from the study that there was a "renewal of growth" rather than mere persistance on the part of the thymus. Hilderbrand (1918) and Blackford (1919) claimed that though enlarged thymus is very common in Graves' disease, the condition is not found in all the cases.

The hypertrophy of the thymus has often been associated with cases of simple congenital goiter. In regions where this disease is endemic, as in Switzerland, Birnbaum (1909) found in the offspring of goitrous mothers an enlargement of both the thymus and thyroid glands. Enlarged thymus showing spontaneous hyperplasia was also noted in young animals by Marine and Lenhart (1909).

Anders (1897), Janney (1918), and others, believe that there is an element of true hypothyroidism in Graves' disease. They also believe that the thymus partially assumes the function of the thyroid when the latter is deficient. Dustin and Zuns (1918), following this supposition, made a comparative study between the weights of the thymus and thyroid glands in normal men who were killed in the war. In general, they were found to be of unequal weight, one is always heavier than the other; if the thyroid weighs more, the thymus then is lesser in weight, and vice-versa.

It is apparent from the search for data that investigators have given very little attention to the relationship between the thyroid and the thymus glands in their experiments. Some of the data obtained are difficult to interpret at present. The results by R. G. Hoskins (1910) on guinea pigs, for instance, show that he observed that the offspring of thyroid-fed female guinea pigs had larger thymus than the normal ones.

Gley (1894) studied the condition of the thymus after the thyroid had been removed and noticed thymic atrophy in a few cases of dogs and rabbits. Similar condition was found by Cadeac and Guinard (1894) in two lambs. Hofmeister (1894), in his rather extensive series of thyroidectomy experiments on young rabbits, obtained negative results. Jeandelize, Lucien, and Parisot (1909) however, noticed in every instance a diminution of thymus weight in the seven young rabbits from which the thyroid was removed. Worms and Pigache (1909) obtained similar results in their experimentation with

thyroidectomized animals. A few days after the thyroid was removed, the thymus degenerated and the parenchymous portion was replaced by connective tissue.

Guedernatsch (1913, 1914) performed some feeding experiments upon tadpoles. He found by feeding tadpoles with thymus extract an opposite effect was produced from those fed with thyroid extract. The tadpoles that were fed with thymus extract grew much faster, but the metamorphosis to the adult frog stage was delayed. In thyroid feeding, the growth was retarded, but the transformation from the tadpole to the frog stage was hastened.

Since the thymus is greatly influenced by nutrition, it is very liable to atrophy in any condition involving malnutrition, thus making it difficult to determine whether the loss of weight after thyroidectomy is due to the absence of the thyroid or to impaired nutrition. E. R. and M. M. Hoskins (1919), in their series of experiments with thyroidectomized tadpoles, found that the thymus continued to grow, and grew relatively large. Since such tadpoles grew rapidly and developed two or three times as large as those in control, H. G. Hoskins (1922) stated that the enlargement of the thymus may be due to nutritional factors. Whether the thyroid and the thymus are connected for a time, at least, is still a question in the minds of investigators. Hoskins (1922) says that no final conclusion can be drawn at present in regards to the definite relationship between the thyroid and the thymus glands.

D. RELATION BETWEEN THYROID AND HYPOPHYSIS

The existence of the relationship between the thyroid and the hypophysis is perhaps the most satisfactorily demonstrated of all the endocrin inter-relationships (Hoskins, 1922).

The rather extensive experimental evidences are fairly well supported by clinical observations. The hypophysis, like the thyroid gland, has a considerable influence upon the metabolic and brain functions, including growth and even life itself. Many of the conflicting results obtained have been due partly to the difficulties involved in surgery; for it was difficult, in former days, to remove the gland without bringing on secondary reactions which might be due to other causes than that of the removal of the hypophysis. (Harrow, 1922).

The pituitary body, like the thyroid gland, consists of two parts or "lobes". It is situated in a depression of a wedge-shaped bone lying at the base of the skull. The anterior portion is said to be more essential to life than the posterior.

Hypertrophy of the pituitary gland after thyroidectomy was first observed by Rogowitsch in 1889. In his attempt to explain this condition he propounded the theory that in case of need the pituitary can, in some degree, assume the function of the thyroid. The following year, 1890, Stieda, repeated Rogowitsch's experiments upon seven rabbits. He described the hypertrophy to be "due to an increase in the number of "chromophobe" cells of the anterior lobe with a vacuolization of their protoplasm". As there did not seem to be any increase in colloid formation, the cells were not markedly affected.

Thyroidectomy was carried out on two dogs by Tizzoni and Sentanni (quoted by Delille, 1909). The results obtained after one and a half and four years, respectively, were similar to those of Rogowitsch, except that the chromophobe cells showed a marked diminution.

The following investigators also obtained similar results in their experimentation with rabbits, dogs, and ram; Gley, 1892; Leonhardt, 1897;

Hofmeister, 1892; Alquier, 1907; Thaon, 1907. Their results were confirmed by Horsley, V. Eiselsberg, and Lusenna (1907).

Cimorini (1907), in his study of dogs and rabbits, noted gross hypertrophy and increased secretory activity in the hypophysis after thyroidectomy in these animals. Herring, in 1908, however, did not find any hypertrophic evidences in the anterior lobe after thyroidectomy. In 1917, Hoskins and Morris, experiemented of frog larvae, but they observed no changes in the hypophysis of these animals after thyroidectomy.

Positive results were later obtained by Rogers (1918), and by Hoskins and Hoskins (1920). When thyroidectomy was performed upon tadpoles, their pituitary glands became much larger in proportion to their body length than the normal tadpoles. The effects produced by thyroidectomy upon puppies and young dogs were studied recently by Kamo (1918). The animals were killed from one and one-half to five months after the operation. The anterior lobes of the gland was particularly affected, a marked hypertrophy to more than two times the normal size.

In 1916, Trautman, made an extensive study of thyroidectomy and its effects upon the hypophysis of 30 goats. He noted marked alterations in three parts of the gland, but Trautman ascribed the changes as being due to degeneration. Signs of over-activity in the pituitary gland were also observed by Sharp (1916), and Mott (1917), when the thyroid was removed. In general, all the evidence seems to indicate rather definitely that the hypophysis becomes hypertrophic in conditions of thyroid deficiency. There is some disagreement, however, as to the degree of affection upon the different portions of the hypophysis.

The effects of thyroidectomy have been more extensively studied than experimental hyperthyroidism upon the hypophysis. Hypertrophy was noted by Guerini (1905), but since he obtained similar results when he

administered pilocarpin and other poisons, he merely regarded the condition as a toxic reaction of the thyroid.

It was observed by Delille (1909) that the hypophysis of rabbits first showed a slight hyperplasia but soon reached a state of exhaustion when treated with thyroid material. E. R. Hoskins (1916) also found some evidence of hypertrophy in the hypophysis of male rats to which thyroid was administered, but a decrease in the hypophyseal weight resulted in the female rats.

From the evidence, there seems to be a rather definite relationship between the thyroid and the hypophysis. If the explanation given by Guerini is to be accepted, (the effect of hyperthyroidism upon the hypophysis), the the theory put forth by Rogowitsch that the hypophysis can vicariously function for the thyroid is fairly well supported. However, the evidence does not exclude the possibility that the thyroid has normally an inhibitory influence upon the hypophysis. The hypertrophic condition associated with hyperthyroidism may be simply due to the removal of this check upon its activity. (Hoskins, 1922).

Livingston, in 1914, and Larson, 1919, have shown by their results that the loss of the thyroid can in a measure be compensated by administering material of the hypophysis. The effect of administration of the anterior lobe substance upon the development of thyroidectomized rats was extensively studied by Larson. He found that the hypothyroid symptoms were very much improved and the life of the subjects can be definitely prolonged. Hoskins and Hoskins (1920), in their experiments with thyroidectomized tadpoles, found that maturity can be promptly brought about by administering hypophyseal substance to them.

E. RELATION BETWEEN THYROID AND PANCREAS

That there is an intimate relationship between the thyroid and the pancreas in regards to carbohydrate metabolism is well known among investigators. Falta's theory was a subject of controversy about a decade ago. His theory was that the adrenals, pancreas, and thyroid, stand in a close triangular relationship. It was assumed that the mobilization of dextrose was facilitated by the inhibitory influence of the thyroid upon the pancreas. Observations made by Underhill and Hillditch (1909) and other later investigators, failed to confirm this theory of Falta. McCurdy (1909) and others showed that the assimilation limit for dextrose is raised by thyroidectomy.

Falta (1909) reported that in a single case, after thyroidectomy, an undoubted hypertrophy of the islands of Langerhans was found. Kojima (1916) and Hoshimoto (1920) have found that thyroid feeding results in hypertrophy of the pancreas.

Hoskins (1922) says, "in view of the highly complicated physiology of carbohydrate metabolism, and of the profound effect which the thyroid has upon the metabolism in general, no conclusion is justified from the data now available as to whether the thyroid gland has any direct influence upon the pancreas as an endocrin organ".

F. RELATION BETWEEN THYROID AND PARATHYROID

The parathyroids were at one time regarded as adjuncts of the thyroid. At present it is quite firmly established that they are independent organs. Gley in his earlier studies on the parathyroids noted that after the thyroid and internal parathyroid glands were removed, the external parathyroid glands hypertrophied and assumed an appearance somewhat like the

thyroid. He concluded that under such conditions the parathyroids may assume the functions of the thyroid; however, after further experimentation, he discarded this view.

Vincent and Jolly (1905), upon examining the parathyroid tissue after the thyroid was removed, found a similarity of the latter gland under the microscope. Similar results were obtained by Halpenny and Thompson (1909) in a dog, and Halpenny later noted a somewhat doubtful instance occuring in a rabbit. That the parathyroids undergo hypertrophy under such circumstances has been confirmed by several subsequent investigators; but, most of the physiologists fail to accept this as satisfactory evidence that the parathyroids assume any function of the thyroid, although this view was maintained for several years by Vincent.

While working further on the problem, Vincent and Arnason (1920) have more recently expressed their doubt on the validity of Vincent's former opinion. The general conclusion reached by the investigators is that the thyroid and parathyroids function independently. It is not definitely known whether the function of one organ influences the activity of the other or not.

VI. CHEMISTRY OF THYROID

A. CHEMICAL ELEMENTS OF NORMAL THYROID

According to Cameron, 1922, the following elements have been reported to be present in a normal thyroid gland; C, H, O, N, S, P, Na, K, Ca, Mg, Si, F, Cl, Br, and I. Zuns (1919) found for the dry and fat-free tissue of normal men killed in war, a nitrogen content varying from 12.46 to 14.82%, a mean value of 13.8% (corresponding to about 4% for fresh

tissue).

Fifty human thyroid glands were examined by Ørgenstern (1912) for Ca, Mg, S, P, and I. The following average was obtained from the results of fresh tissue; Ca, 0.4%; S, 0.2%; P, 0.19%; Cl, 0.25%; I, 0.013% (this last was not found in eight cases).

Fenger (1913) examined exhaustively the P content of beef thyroid glands, and, found that the average P content for nearly 4,000 beef thyroids was 0.4%, dry tissue, or 0.12% for fresh tissue. The results obtained from the dried glands of human fetuses were 0.72% and 0.79%, male and female respectively.

Schulz (1912) found the average silicon content of normal human thyroids to be 0.0082%. Gautier (1913) found arsenic in fresh thyroid tissue, 0.00005 to 0.0009%. Hodlmoser, however, denied the presence of this substance.

Bromin was found to be present from 0.00007 to 0.003% for fresh tissue by Labat (1913) in his examination of 16 out of 24 human thyroids.

Gautier and Clausmann, in 1913, found 0.00054% of fluorin in fresh human thyroids and 0.00046% in fresh sheep's thyroids. The percentages for the dry tissues were 0.00212 and 0.00162%.

Macadam (1854) having demonstrated that iodin was present in a number of edible plants, concluded that it should be present in the higher mammals, including man, but he was unable to detect its presence. It was suggested by Kocher in 1895 that iodin might be a constituent of the gland, since beneficial effects have been obtained when patients suffering from cachexia thyropriva were treated with thyroid extract and iodin. Following his suggestion, Tshirsch (1895) tested the thyroid gland for iodin, iodides, and iodates. He obtained negative results.

According to Halsey (Barker's "Endocrinology", I, 1922, P. 84),

the real beginning in our knowledge about the chemistry of the thyroid was Baumann's discovery of iodin in the thyroid gland, in 1895. Almost immediately after Tshirsch's observations, he announced his discovery of iodin in the thyroid. Its presence was detected in sheep and human thyroid glands, and in a smaller amount in goitrous gland and pig's thyroids. The following year, 1896, while examining a large number of human thyroids, he found extreme variations, from a trace to 0.46% of iodin in dry tissue, the average content was 0.09%. In many of the children's thyroids examined by Baumann, he found that iodin was absent and if present, usually in very small quantity. Iodin was found in the thyroid glands of horses, cattle, dogs, swine, and rabbits.

The various experiments that have been performed since, all confirmed the results obtained by Baumann, in 1895. Due to improved chemical methods, many of the smaller quantities which were formerly not detected have now been proved to be present in organic matter. Iodin is found in normal thyroid tissue of all vertebrates.

Fenger, 1914, found ash in beef thyroids; about 45% in dry tissue, and 1.2% in the fresh tissue.

B. COMPOUNDS PRESENT IN NORMAL THYROID

1. Water

The ratio of the weight of fresh to dry tissue varies between the limits of 3:1 and 6:1 (66 to 85% of water). The variations seem to depend to a certain extent on the species but to a greater extent on the age of the subject. Castration lowers the water content, though sex does not seem to show any apparent influence. The effect of age is shown in the following percentage figures for cattle obtained by Fenger, 1912: 84%, for

fetuses three months old; 82.3%, for fetuses seven to eight months old; 74%, for calves six to eight weeks old; and 72.6%, for adults.

Seasonal variations in water content are shown in the figures of Seidell and Fenger (b) 1913, the percentage being lower in summer.

2. Intermediate or End Products of Metabolism

According to Cameron (1922), the following compounds are found in the tissue of the thyroid gland: urea, lactic acid, cholin, leucin, volatile fatty acids, hypoxanthin, xanthin, succinic acid, and creatin. These compounds are also present normally in the different tissues of the body.

3. Carbohydrates

Glycogen has been found to be present on an average of 0.27%, (Marie Ramberg and de Kieselbach, 1911). Maranon (1916) ststes that the amount is similar to that found in the suprarenal glands. Grund (1902) observed that dried beef thyroids contain 0.5% of bound pentose.

4. Fats and Lipoids

A number of different lipoids have been found by Iscovesco (1913) in the thyroids of sheep, up to a maximum of 15% of the dried gland. One of these, soluble in petroleum ether, and insoluble in acetone, is stated to have marked effects on general growth; it stimulates the growth of growing rabbits, but decreases the weight of adults and produces a definite hypertrophy of specific organs.

Fat is the shief petroleum ether-soluble portion of beef thyroids. It has been obtained from several hundred animals and averages 4.2% of the

fresh gland, (which contains 75.5% of water) and of this, Fenger, (1916) found 0.13% to consist of phosphatids which were believed to be lecithin. There is a marked contrast between the thyroid and other ductless glands in that the thyroid does not contain any more phosphatides than the ordinary muscle fiber. The other ductless glands all contain a much larger quantity. In Fenger's opinion, this indicates that the lipoids do not play an important part in the internal chemistry of the thyroid.

5. Proteins

Oswald (1897) isolated two proteins, iodothyroglobulin and nucleoglobulin. These are the only two definite proteins that have been isolated.

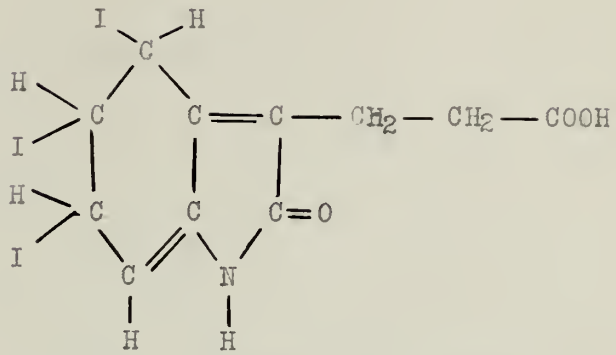
6. Enzymes

Investigators have found that the thyroid gland contains a lipase, a catalase, and that it is relatively rich in nuclease. The lower esters of the fatty acids are strongly acted upon the lipase. It acts less strongly upon the natural fats. The lipase obtained from carnivorous animals is more active than that from the herbivorous types. It is readily extracted by water but only to a certain extent by glycerol (Yushchenko (1910, L911). Goldenberg (1917) found the presence of an oxidase in the thyroid tissue.

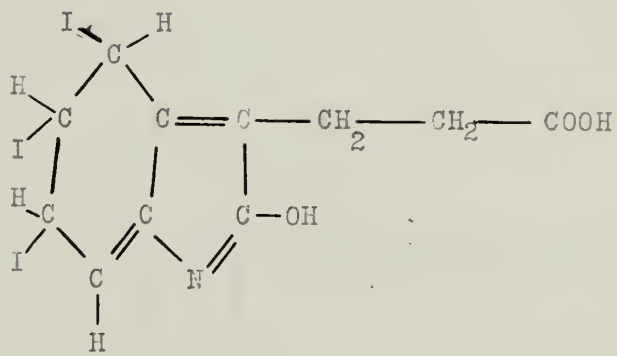
C. FORMS OF IODIN COMBINATION IN THYROID

Thyroxin is a crystalline substamce isolated by Kendall, in 1915. It contains 60% iodin and is said to be 4-5-6- trihydro- 4-5-6 triiodo-2 oxybeta-indole propionic acid. It is found in three forms: (1) the keto form with the carbonyl group adjacent to the imino; (2) a tautomeric enol form; and (3) an open ring structure. Thyroxin can be regarded as derivative of

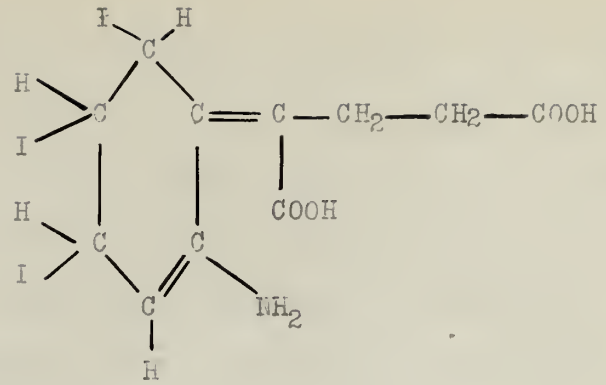
trytophan, and is thought by Kendall to occur in the body in the third form. It is very easily changed to the open ring form in the presence of certain hydrolyzed protein products, which contain the indol nucleus.



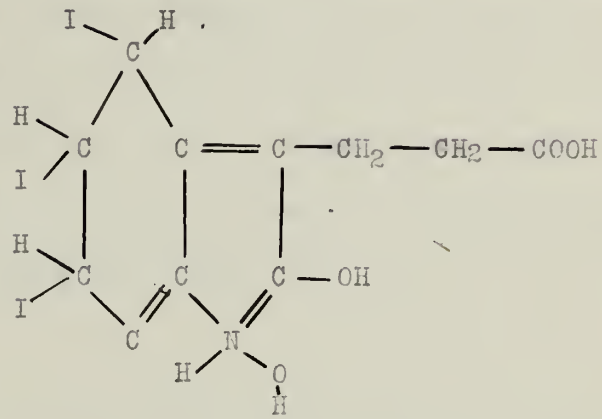
(1) Keto Form



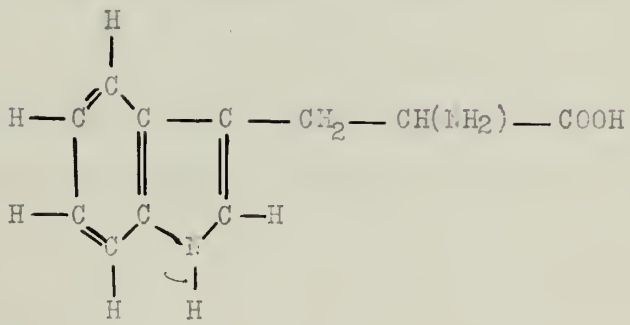
(2) Enol Form



(3) Open Ring Form



(4) Amino-hydrate



(5) Tryptophan

1. Keto Form

In the keto form, thyroxin is a white, highly crystallizable substance (needles), odorless, and tasteless. It is found in this form in an acid solution. Except in strong acid or base, it is insoluble in organic solvents. In the presence of a mineral acid or alkali, it is soluble in alcohol. It has an empirical formula of C_{11} H_{10} O_3 NI_3. The melting point is about 250 degrees C., and is very stable when exposed to heat. It is also amphoteric and has a molecular weight of 585.

In the presence of the imino group, it gives rise to salts very readily. The salts, such as sulphate, hydrochlorid, and a uerid (HCNO), an acetyl derivative with acetic anhydrid, are all crystalline compounds. Thyroxin yields crystalline mono-salts as Na, K, and NH_4; and di-salts Na, K, NH_4, Ba, Ca, Mg, Ni, Zn, and Cu. These can scarcely be obtained in a pure form, because they decompose so readily. Decomposition takes place even when it is being boiled with water.

2. Enol Form

The second or enol form is found existing in an alkaline solution. This form can be prepared by cold hydrolysis of the ammonium salt, a solution in pyridin, and an addition of water; it then separates in rosettes or in sheaves of short needles with a melting point of 204 degrees C. It changes very easily into the keto form. The enol form is readily soluble in anhydrous or aqueous pyridin and quinolin and in formic acid.

3. The Open Ring Form

The open ring form is soluble in alcohol, changing in the

solution to the keto form. This from can be prepared by adding sulfuric acid to an alkaline aqueous solution of thyroxin; the precipitate is then removed from the solution, suspended in distilled water, and boiled. The thyroxin then precipitates in long bundle-blades and has a melting point of 225 degrees C.

4. Amino-hydrate Form

By heating an alkaline solution of thyroxin and adding 10% ammonium chlorid, an "amino-hydrate" form can be easily produced. The melting point is 216 degrees C. If the five, separated, branching crystals are suspended in distilled water containing a small amount of formic acid, and the suspension boiled, the crystals will be changed to the open ring form.

VII. PHYSIOLOGICAL PROPERTIES OF THYROID SECRETIONS

A. IODOTHYRIN

Iodothyrin is said to have all the characteristic properties of the thyroid, and to produce more rapid physiological action than the fresh gland or tablets. (Baumann and Roos, 1895). It is stated by Baumann and Goldmann (1896) that it prevents the appearance of cachexia thyreopriva in thyroidectomized dogs. In 1896, Roos found in his experiments with a dog, a loss of weight, a rise in nitrogen excretion, and a doubtful rise in phosphorus excretion. Many other investigators have worked with it also, but there does not seem to be any uniformity of results, due probably to the different methods of preparation. Cameron (1922) says that "it would seem certain that if iodothyrin does possess some physiological and metabolic activity, it does so to a very much less extent than thyroid itself".

Iodin-containing peptones and proteoses derived from the thyroid

do not possess the physiological properties of iodothyrin. Cyon and Oswald (1900) found that they have no thyroid action on the blood pressure and heart beat. Asher and Abelin (1917) obtained a thyroid preparation which is soluble in water, but which is free from protein and contains little iodin. This substance exerted the same physiological and metabolic effects as the whole thyroid gland.

B. IODOTHYROGLOBULIN

Oswald, in 1916, studied the physiological properties of iodothyroglobulin more exactly and found that this substance with its methylene derivative is very much like the thyroid. In 1899 he quotes Magnus-Levy as an authority for the cure of myxedema by the administration of iodothyroglobulin. In administering it to a dog (1901) Oswald observed it had a specific effect on blood pressure and pulse. Others have used it on cachexia thyreopriva as a test, and they found that iodothyroglobulin resembles thyroid while iodothyrin does not.

C. THYROXIN

Kendall (1919) found that thyroxin when injected into the body produces the same effects as thet produced by the thyroid. There is a delay in the action of thyroxin; successive daily administration brings about death, but a single injection even of enormous doses, produces no effect. Thyroxin increases the basal metabolic rate and according to Plummer (quoted by Vincent, 1922) 1 mg. of thyroxin in an adult weighing 150 pounds increases the metabolic rate 2%. Kendall believes that thyroxin is a catalyst, the activity being caused by the CO-NH group, and that thyroxin relieves all the symptoms of cretinism and myxedema in the same manner as desiccated thyroid tissue (1918). Janney (1917) observed that in normal individuals

the nitrogen excretion was increased and the physiological symptoms were similar to those produced by overdoses of thyroid; a decrease in the growth rate and hypertrophy of body organs. This has been carried out in experiments with rats, showing that thyroxin is identical with the essential compound secreted by the thyroid gland. (Cameron and Carmichael, 1921). Though evidences seem to show that thyroxin is one of the active compounds secreted by the thyroid, it cannot be definitely stated that it is the only specific compound, for other hydrolyzed products possess some physiological activity. (Cameron, 1922).

VIII. PATHOLOGICAL CONDITIONS OF THE THYROID

A. HYPOTHYROIDISM

Myxedema is usually applied as synonymous with severe hypothyroidism in adults, and refers especially to the peculair thickened cutaneous areas. Strictly speaking, myxedema is but a single symptom of hypothyroidism. In connection with this, the term "cretin" signifies a small hypothyroid individual.

1. Pathological Condition of the Thyroid in Hypothyroidism

The lesions in hypothyroidism are in the gland itself, but the effects are felt by all organs and tissues of the body. Kacher (1906) says, "without lesions or absence of the thyroid, no myxedema". The gland may show hyperplastic processes such as goiter, or hyperplasia. According to recent views in the discussion of the pathogenesis of goiter, all hyperplasia of the thyroid is due to thyroid insufficiency. The goiters of sporadic hypothyroidism may be simple and small and, when larger, often

show cystic and other retrogressive changes. There is no essential difference from that of endemic goiter.

The atrophic changes of the thyroid are the most important feature of sporadic hypothyroidism. A complete atrophy is observed in children developing this disease. The alveoli are reduced in size and the number of cells is decreased while the round cells increase until all the glandular substance of the cell has disappeared. After this, a complete, fatty degeneration takes place. According to the English Myxedema Commission, then, the pathological process is a chronic outgrowth of connective tissue.

Marine and Lenhart (1911, f) describe carefully the histo-pathological changes in myxedema in the following paragraph:

"The colloid is practically absent. The epithelial cells have lost their regular and uniform columnar type characteristic of the early stage of active hyperplasia and are irregular in size and shape. There is perhaps some piling up of the epithelial cells and desquamation of the partially degenerated cells. The nuclei are in general large, and often hyperchromatic and irregular in size and outline. Nuclear figures are still observed, but the new formation of cells is not sufficient to offset the cell-death and the follicles become smaller, though still preserving the infoldings of the well-developed hyperplasia. The surrounding fibrous stroma is relatively, perhaps absolutely, increased, as the follicles become smaller from the death of their secreting cells the fibrous bands appear wider, and finally give the appearance of a generalized cirrhosis in which are nests of compressed epithelial cells with or without the outlines of follicles. This interstial cirrhosis is secondary to and consequent to the death of the epithelial elements.

Lymphoid foci are scattered here and there throughout the stroma. This is the simplest picture of the anatomical changes in the thyroid in myxedema, and those occurring in the cretin thyroid are similar. Most cases, either of myxedema or of cretinism, in man, do not present so simple an anatomical picture for the reason that other processes as cyst formation, hemorrhage, calcification, adenoma, groups of enlarged follicles filled with desiccated colloid, etc., may all be crowded into the same gland.

"Summing up, then, the type of atrophy suprevening on active hyperplasias and clinically associated with myxedema or cretinism is a cell-death due to exhaustion from overwork and malnutrition. The process is simple, but the anatomical changes in such glands, especially in long-standing cases, are often highly complex".

2. Myxedema

a. Description

The term "myxedema" is now in general used for a collection of symptoms caused by the loss of thyroid function after the individual is fifteen years of age. In the primary cases of myxedema, the loss of function in a majority of cases is due to chronic fibrosis with atrophy of the gland. In cachexia strumipriva, or secondary myxedema, the symptoms are due to the removal of the gland by operation for the disease. Myxedema occurring in infancy or childhood is called "cretinism", or infantile myxedema.

b. History

According to Murray (1900), the history of myxedema is short, but it is an eventful one. Attention was called to this disease by Sir William Gull about fifty-seven years ago. He described the symptoms of the disease in his paper, "On a Cretinoid State Supervening in Adult Life in Women", before the Clinical Society of London in 1873.

Dr. W. M. Ord (1877) recorded five clinical symptoms; a post-mortem description of one of them is given by Greenfield (1893), and the chemical examination results of the swollen skin was made by Charles. The condition of the thyroid was described, showing an advanced fibrosis of the gland. Ord found an excess of mucin in the oedematous skin and called the condition "myxedema". Charcot (1881) proposed the name "cachexia pachydermique". Many cases have since been observed and recorded. Reverdin (1882) recorded a chain of symptoms which he noticed after the thyroid was removed for goiter. Kocher (1883), in the following year, observed similar symptoms and called the condition "cachexia strumipriva". At that time he believed it to be a result of a chronic asphyxia, caused by injuries to the structures in the neck during the operation, and not to the loss of the thyroid gland. Soon after that, Semon (1888) suggested that the conditions were similar in both cases, and the symptoms in each case were due to the loss of the thyroid. Following this suggestion, a special committee was appointed by the Clinical Society of London to investigate the matter thoroughly.

Horsley conducted the experimental part and showed that cachexia strumipriva was caused by the loss of the thyroid function resulting from the removal of the gland alone. A very detailed account of the investigation was given by the committee. The conclusions were:

(1) the conditions of myxedema and cachexia strumipriva are identical; (2) the sporadic cretinic condition is myxedema of childhood; (3) endemic cretinism is closely related to myxedema, and that, though the conditions are due to the loss of the thyroid function when it is removed or diseased, the ultimate cause of the loss of function in ordinary myxedema is not yet explained.

When the causation of the symptoms was better known, advances were made in the direction of rational treatment. Various thyroidectomy experiments then followed. Schiff (1884) proved that the usual fatal effects after thyroidectomy in dogs could be avoided by a previous transplantation of another thyroid into the abdomen. This has also been found true for cats. Horsley (1890) suggested that myxedema in man may be treated by thyroid grafting. Acting upon this suggestion, Serrano and Bettencourt, observed marked improvement in their patient directly after the operation. The improvement was attributed to the absorption of the juice of the gland. Early in 1891, Murray suggested that the extract might be used as a remedy for myxedema. Through continued administration, by hypodermic injection, he was able to prove the disappearance of the symptoms of the disease. Other investigators obtained the same results by giving the raw gland, or some preparation of it, by the mouth.

c. Primary Myxedema

(1) Etiology

The symptoms of primary myxedema are due to the loss of thyroid function, which is a result of slowly developed fibrosis. The intensity of the symptoms is variable, depending upon the degree of

fibrosis and the amount of atrophy of the glandular structure. Myxedema may develop at any age, from infancy to old age. It is called cretinism if developed in childhood. The disease is more common in women than in men, occurring from the ages of 15 to 70. Generally speaking, it is a disease of cold and temperate climates. Social position does not seem to have any influence upon its development.

(2) Symptoms

The onset of the symptoms is so very gradual that it is difficult to fix the exact time for the beginning of the disease (Murray, 1900). During the eraly stages of this disease, there is a gradual increase in languor, sensitiveness to cold is also increased, so that when these two symptoms are combined, the patient may be led to adopt an indoor life of mental and physical inactivity. Frontal head-ache is felt by some as an early symptom.

The subcutaneous tissues begin to swell around the face, especially beneath the eyelids and chin. The skin becomes yellowish and dry, and transverse wrinkles on the forehead may appear. These changes are accomplished by an increase in size and weight, sometimes wrongly thought to be obesity.

The most striking characteristic of myxedema is seen in the solid oedema of the subcutaneous tissues. There is marked swelling of the face, backs of the hands, but little swelling of the parts where the skin is more firmly fixed to the structures, as in the palms or scalp. Thus, as in the illustration, (see page 46) the woman appears to be very fat, but, on careful examination, it is found that she is myxedematous.

Myxoedema with Obesity

(Fig. 16, opposite page 42, "Disease of the Thyroid Gland", Murray).

Many of the fat women of the stage are said to be of this type. The swelling often impedes the movement of the limbs. The lips become thick and are often everted; there may also be considerable swelling beneath the chin and around the neck so that the supraclavicular fossae are partly filled up by this swelling. The swelling of the trunk and limbs is fairly uniform, though in some cases the extremities may be much larger in proportion. The external genetalia may be swollen or of normal size.

Due to the swelling, the thyroid, in many cases, cannot be felt at all. Even after treatment, it is hard to determine the size of the gland. When the gland is found, it is, in the majority of cases, smaller than when one is in health.

The hair of the head becomes thin and scanty and, in many cases, results in complete baldness. The nails are often cracked and discolored. The teeth become brittle and carious.

The temperature may remain normal, or fall to 66 to 77 degrees, or may be from 93 to 95 degrees F. There is a general slowness in the execution of functions which are controlled by the nervous system. A change in the mental condition can also be detected; the patient learns slowly and is very subnormal in thought and action.

Hallucinations frequently occur in advanced cases and, when not treated, will develop into insanity. Palpitation, dyspnoea on exertion, and attacks of syncope, are symptoms commonly associated with advanced myxedema. The weakness of the heart is caused by the degenerative changes in the muscular walls; it ia therefore not able to withstand any undue strain.

d. Secondary Myxedema

Secondary myxedema is sometimes known as cachexia strumipriva, or operative myxedema. In the extirpation experiments performed upon the animals, it has been observed that definite symptoms of myxedema are produced. This is also true of man. Reverdin (1882) and Kocher (1883) have given complete accounts of the symptoms produced by thyroidectomy. The development of secondary myxedema is identical with that of primary myxedema. resulting in fibrosis with the atrophy of the gland.

The symptoms of cachexia appear frequently after the patient has recovered from the immediate effects of the operation. In some cases, changes have not been observed until four to five months have passed. From the data collected from a number of surgeons by the committee of the Clinical Society, it was shown that cachexia strumipriva developed in one-third of the cases in which all the active thyroid tissue was removed, and only a few cases after partial thyroidectomy. Secondary myxedema now rarely occurs in man, because through experience it is found that a certain amount of the gland is necessary to produce an adequate supply of the secretion. If complete thyroidectomy is necessary myxedema is prevented by continuous thyroid feeding.

(1) Treatment

Primary and secondary myxedema are due to the loss of function of the thyroid. The symptoms can therefore be removed by giving the patient a sufficient supply of the gland secretion. When all the symptoms have disappeared, the patient must take a daily dose

of the thyroid extract as long as he lives. The dose is equivalent to the daily output of the normal thyroid gland.

3. Cretinism

a. Description

The term "cretinism" here is used to denote myxedema occurring in infancy or in childhood before the age of fifteen. The symptoms are due to destructive disease or arrest of development of the thyroid gland. In additon to the symptoms occurring in adult myxedema, there is an arrest of mental and bodily development.

There are two forms of cretinism, endemic and sporadic. The causes are alike, being a loss or diminution of thyroid function due to disease of that organ. The severity of the symptoms depends upon the degree of destruction of the gland by the disease.

b. Etiology

The causes of cretinism, according to Murray (1900), may be due to (1) the absence of the thyroid, (2) an arrest of its development, (3) fibrosis, with atrophy of the glandular substance, (4) conversion into goiter, and (5) removal by operation.

Cretinism develops any time between birth and fifteen years of age. Generally, nothing abnormal about the child is noticed at birth. In some cases, the symptoms do not attract any attention during the first three or four years, and even in exceptional cases, up to the eighth or twelfth years.

It is more common in females than in males. Sporadic

cretinism does not appear in two successive generations, because both sexes are nearly always sterile. Sporadic cretinism, unlike the endemic form, is not confined to any one locality; it is found in Europe, America, and Australia. Locality plays an important part in endemic cretinism; it is most frequently confined to the narrow valleys of mountainous regions of Europe and Asia. The cause of both endemic goiter and sporadic cretinism is probably identical. The drinking water seems to be a cause for both conditions.

c. Symptoms

The appearance of a cretin is unique and striking, and may be recognized at once in advanced cases. The child is very inactive and sits in one position many minutes at a stretch without doing anything. It takes no interest in its surroundings. It may, however, be aroused from this state by the sight of food or a familiar face.

Young cretins are dull, placid, and inactive. Some are so deficient in mental powers that they remain idiots. The more intelligent ones may learn a few words, have clean habits, and be able to feed themselves. The facial expression is stolid and fixed, though most cretins are easily amused. When cretins are able to walk, their movements are slow and awkward.

d. General Appearance and Condition

The whole body is short and stunted, the characteristic becoming more striking as the patient increases in age. General subcutaneous solid oedema is present, the amount is variable in different cases. The swelling is most evident where the subcutaneous tissues are

flabby, such as in the eyelids, lips, cheeks, and neck, and especially in the supraclavicular fossae. Definite rounded swellings are often formed in these fossae, sometimes called "fatty tumors" on each side of the neck. The head is narrow in front and broad behind. The face has a general rounded appearance, due to the swelling of the cheeks and chin. The nose is short and broad, depressed at the bridge, turned up at the tip, and with large, dilated nostrils. The mouth looks large and is generally opened. The lips are thick and everted with a large swollen tongue protruding between. The ears are large and prominent. The skin is dry, rough, and cold. The scalp is rough and generally covered with coarse hair.

The abdomen is large and prominent, and, in many cases, either an umbilical or inguinal hernia is present. The limbs are short, the hands and feet are especially broad and thick.

A picture of extreme repulsive ugliness is seen in adult cretins. The illustration on page 52, is of a typical cretin, a woman of twenty years, first observed in June, 1895. During infancy, her mother noticed that her extremities became blue and cold after being bathed, and that her abdomen was prominent. Growth stopped at nine months old, after a fall in which her back was hurt, and the symptoms of cretinism gradually developed. Systematic treatment was given at once, and the amazing results may be seen in the illustration at the lower right corner of the page. If treatments are given in the early stages of the disease, all the symptoms will disappear, and mental development is likely to take place in proportion with the bodily improvements.

Cretin, Before Treatment, Aged 28,
June, 1895; Height, 34½ in.

(Fig. 24, opposite page 94)*

Cretin, After Treatment, Feb., 1899;
Height, 38½ in.

(Fig.25, facing page 107)*

*"Disease of the Thyroid Gland", G.R.Murray, 1900.

B. HYPERTHYROIDISM

According to Howard (1922), the term, "hyperthyroidism", is a comparatively recent one which is used to indicate a hyperfunction of the thyroid. "Exophthalmic goiter" falls under this classification of hyperthyroidism. The only distinction between simple thyroidism and exophthalmic goiter is that in the former both the goiter and the exophthalmos may be absent at the time of observation. There are twenty-one synonyms for exophthalmic goiter; the most commonly used ones are Graves' disease and Basedow's disease.

1. Pathological Conditons of the Thyroid in Hyperthyroidism

Four theories have been advanced to explain the conditions which bring on the disease. None of these will be discussed in detail here, as there are so many differences of opinion as to their worth. Pierre Marie (1883) cleverly states that, "there are in pathogenesis, as in therapy, many theories but little truth".

a. The Toxic Theory

The toxic theory was advanced by Marine and others before him, presupposing that there is a chemical alteration of the water supply. There is quite a difference of opinion as to the relative geographical distribution of the endemic form of goiter and exophthalmic goiter.

b. The Infectious Theory

The infectious theory claims that the water supply is infected by Bacillus coli communis or an auto-infection of the patient

by the normal bacterial flora of his intestinal tract. Neither of these two theories is universally accepted. No substantial evidence has been found at present to support these theories.

c. Thyrogenic Theory

Rehn first outlined this theory in 1883, and later in 1896, Moebius elaborated it into the present form. This theory supposes an intoxication from a morbid or excessive production of the thyroid secretion, or, in Moebius' own words, "Graves' disease is an intoxication of the body by a morbid activity of the thyroid gland". It is supported by clinical and experimental results such as: (1) the contrast shown by the conditions of hypothyroidism and hyperthyroidism; (2) results shown by thyroid administrations; (3) results of thyroidectomy in Graves' disease; and (4) microscopic changes of the gland when diseased. This theory has been accepted by such European investigators as Gibson, Murray, MacKenzie, Mueller and Kocher.

d. Neurogenic Theory

The neurogenic theory claims that exophthalmia affects the ganglia of the sympathetic nervous system as demonstrated in the symptoms of the disease, resulting in a paralysis, or a state of irritation.

Crile (1913, a, b) recently advanced another theory, called the "Kinetic Theory", Howard (1922) calls it a "romantic theory" and at present "too theoretical and lacking in scientific confirmation".

2. Etiology

As in the case of hypothyroidism, women are much more frequently affected than men. The age of greatest susceptibility is between sixteen and forty. It is rarely found after the fiftieth year. A predisposition to the disease seems to be present in certain families. Many investigators have emphasized the association of fright and mental activity with the disease. The prolonged use of thyroid extract or iodin has been frequently a cause of hyperthyroidism. There are many cases in the literature showing the effects of acute thyroid poisoning after prolonged or excessive use of thyroid tablets. The cases show palpitation, tachycardia, tremor, nervousness, sweating, and gastro-intestinal irritation, but never exophthalmos or goiter.

3. Symptoms

The symptoms are said to involve every system of the body. Howard (1922) presents five cardinal symptoms: (1) goiter, (2) exophthalmos, (3) tremor, (4) tachycardia, and (5) increased metabolism.

A person suffering from exophthalmic goiter almost always has an enlarged goiter, though the increase in size may not be great. The right lobe is usually more enlarged than the other. The surface of the gland feels granular, and its consistency, though firm and elastic, is rarely hard. It is sometimes even soft and elastic.

The heart action is at times very distressing. There is often a feeling of suffocation or swelling in the throat. In the hyperthyroid heart, and in fully developed exophthalmic goiter, the pulsation is felt over the region of the right ventricle. The carotid and brachials may pulsate

violently. The blood pressure is usually low. An autopsy examination will reveal marked hypertrophy and dilation of the right ventricle.

It is said that the circulatory system suffers more than any other system of the body in exophthalmic goiter. In the advanced cases, the pulse rate may range from 100 to 180, or even 200 beats per minute. Dock (1906) has found in one of his cases a rate of 225 beats which continued for several hours. Physical exertion increases the tachycardia, but an emotional stimulus increases it still more. The rapid heart action is due to the stimulation of the accelerator nerve of the heart through the sympathetic nerve by the action of thyroid intoxication.

The eyeballs usually protrude. The protrusion is often a late sign of the disease. The condition may sometimes exist for years without being detected. It may develop suddenly, however, in very acute cases. The eyeball in the beginning may be easily pushed by gentle pressure, but, as the disease advances, the eyeball remains fixed in the forward position, due to the fatty tissue in the orbit.

The skin is very pale, thin, soft, and satiny to touch. It is always moist and, under marked excitement, is bathed with profuse sweat. The teeth show a rapid decay.

4. Treatment.

The treatments of exophthalmic goiter are numerous. Some believe that it can be cured by non-surgical methods. There are two methods, the general, and the local methods of treatments. The measures briefly for each are: General measures; (1) rest, (2) fresh air, (3) electricity. and hydrotherapy, (4) dietic, (5) medicinal, (6) organotherapy and

and serum therapy. Local measures; (1) cold applications, (2) X-ray and radium, (3) injections and surgical procedures.

C. GEOGRPHIC DISTRIBUTION

Thyroid diseases may occur in all countries and among all races, though the Negroes and the Chinese are rarely affected. Cases have been more frequently found in cold climates (Janney, 1922).

The following figures are taken from Falta* who had taken them mostly from Ewald and E. Bircher. It was found that 7.2% of the applicants for military service in Switzerland were rejected on account of having goiter; and later, 2% more were discharged. In Cisleithania, there were 71 cretins for every 100,000 inhabitants. In Murrau and Steiermark, and other strongly infected districts, there are more than 1000 cretins per 100,000 inhabitants. About 1% of the population of France in 1873 were goitrous; and 0.3% were cretins and idiots. In Piedmont in 1883, about 0.15% were cretins; and in Lombardy, about 0.2%. According to Falta, the etiology of this affection is not yet known. A study of geographic distribution, however, shows that goiter, endemic cretinism, goiter heart, and endemic mutism, belong together. Their parallelism in distribution has been convincingly shown by some investigators. It has been observed that cretins almost always are goiter carriers.

Cretinic degeneration is found in Europe, especially in the Alps. Large goitrous districts are found in the Carpathians, the German Mittelgebirge and the Pyrenees. As in the other parts of the world,

*Falta & Meyers, "Endocrine Diseases", 3rd ed., p.164-165, 181.

most of the goiter districts of Europe lie in the mountainous regions. The distribution of this disease may change, however, localities once infected may become goiter-free, but another district may carry on the infection. The disease may sometimes break out in the form of an epidemic. Goiter is sometimes developed by persons who come from a goiter-free district into one that is infected with this disease, or develop it after they return to their former home. E. Bircher cited an example:

He observed that in a goiter-free locality a particular family had healthy children, but when they moved to a goiter district, a cretin child was born. The parents were not affected. Kocher reported a similar case:

The parents and their nine children remained healthy as long as they lived in a non-goitrous district. When they changed, however, to a goiter neighborhood, three cretin children were born, the first one being the most pronouncedly affected. The thirteenth child was normal, but very small. If the families are removed from the goiter regions, they are able to recover from the infection. Enormous goiter outbreaks have also been observed in regiments which have been stationed in infected regions (Breitner).

Some investigators claimed that in the goiter territories there are special goiter brooks, which contain the "noxus" of goiter in the water. In the earlier literature there are numerous examples showing that a goiter community has become goiter-free by changing their source of water supply. Recent investigations show that goiter can develop in the communities having the purest water supplies, (Marine and Kimball, 1921) and is thus regarded as being caused by a lack of iodin in the water supply of these regions.

In the United States, goiter is not an uncommon disease. The occurrence is, however, confined to certain districts. Endemic goiter was found by Clark and Pierce (1914) to be in the region of the Great Lakes and certain sections of West Virginia. Mayo (1921) says: "There is a tremendous amount of goiter in this country. Comparatively few of the cases occur in New England or in the Southern States. There were about three cases of goiter to each 1000 of draft recruits in the district of New York, seven cases to 1000 in the Great Lake region, eight to nine cases to 1000 in Montana, and fourteen cases to 1000 in Oregon, Washington and Idaho. The incidence of exophthalmic goiter, three to 1000, as noted by some Western Draft Boards of the Army is too high for men in the third decade, since most exophthalmic goiters occur in women",

IX. SUMMARY

Formerly, the thyroid was thought to be insignificant to the vital processes of the body. Since its importance has been recognized, it has attracted much more interest. At present, there is no doubt but that the thyroid is a ductless gland. Due to the absence of a canal, the only possibility for the colloid secretion to enter the circulatory system of the body is either directly or by means of the lymphatic syatem.

Recent investigations have shown that the thyroid is a compound structure. It is closely related anatomically to four nodules having a different type of tissue, the parathyroids. These probably have a chemistry of their own and function independently, though they have a close relation

The importance of the thyroid gland varies with different animals. While some are apparently able to live without it, others may suffer severely when it is removed, or when the gland is not functioning properly.

Frequently, the thyroid may be enlarged causing disfiguring swellings in the neck region. The swelling is commonly called a goiter and is a hyperthyroidic condition. Sometimes the swellings may not be associated with any general disturbances of the health of an individual. In many cases however, disturbances are observed, and the developing symptoms are said to be due to an overactivity of the glandular substance. Generally, breathlessness, palpitation, a marked loss of weight, and extreme nervousness are observed. These symptoms may also be observed when an overdose of thyroid extract is given to an individual. Some investigators have tried to use this extract as a means of reducing obesity. The disadvantages of using such a powerful drug for the treatment of this condition are numerous, besides, the success of its use in such cases is questioned by some of the investigators.

Just as there may be more thyroid substance than is good for one, so may there be a lack of it. When the thyroid gland fails to function properly, various symptoms result, and a definite disease is caused in human subjects. In the experimental animals, a complete removal of the gland is often followed by a decided decline in the physiological activities of the body, if not by death. The scientific data and results all show that the development and well-being of the subject is dependent to a large extent upon the normal functioning of the thyroid gland.

Many of the current views concerning endocrine secretions in general have been somewhat altered since the discovery of "hormones".

Kendall claims that the physiological action of the thyroid substance is probably like that of a catalytic agent. The catalytic agent is the iodin present in certain organic combination which aids in the fundamental metabolic activities of the body.

The remedial properties of the thyroid substance is said to be thyroxin, a compound isolated and named by Kendall. This substance has been administered to patients suffering from hypothyroidism, especially myxedema, by various means, and the effects carefully observed. It was found that a single large dose produced no ill-effects, while successive small doses caused death to the subject. When it was administered intravenously, a marked fall in blood pressure resulted; the effect, however, was temporary.

The physiological effects of the thyroid on the development of rats and tadpoles were studied by thyroid feeding. Soon after the substance was fed to tadpoles, it was observed that growth was suppressed, though the metamorphic process was hastened. Though the administration of iodid produced no ill effects on white rats, the thyroid feeding, retarded their growth. It has been shown experimentally that thyroid feeding does not produce exophthalmos, tachycardia, or nervousness. The symptoms may be those of hyperthyroidism, but they are not those of exophthalmic goiter. Man is said to be very susceptible to thyroid feeding.

Some investigators claim that the substance of the thyroid is toxic, but how much of the toxicity is caused by iodin is not definitely known at present. Swingle (1918 and 1919) states that all the hypothyroidic symtpoms can be produced in thyroidectomized tadpoles by

overfeeding them with iodin, but it is quite likely that this does not apply to man.

When administered by skillful persons, thyroid extract or any special iodin preparation has produced remarkable results. The changes can be felt by the patient within a few hours after the extract has been taken. I was fortunate to come in direct contact with some thyroid patients while I was preparing this paper. One of the most interesting cases was one that received a "Lugol" treatment, which is a special preparation of iodin, for an abnormal function of the thyroid, and the physiological effects produced on the general health of the individual by two or three drops of the preparation twice a day are miraculous. This substance must not be confused with thyroxin, which produces very different effects when it is administered to an individual.

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Note:

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I have carefully read the various articles in as much as they are related to the subject.